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Prevention of head louse infestation: A randomised, double-blind, cross-over study of a novel concept product, 1% 1,2-octandiol spray versus placebo.

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ABSTRACT

Background: Despite innovations in treating head louse infestation families face repeated problems from lice in the community. Most people would prefer prevention of infestation but there is little evidence for the effectiveness of conventional insect repellents. However, 1,2-octanediol has been shown to kill lice at low levels as a residue on hair.

Design: Randomised, double blind, cross-over.

Setting: Use in the community in Cambridgeshire, UK.

Participants: 63 male and female children, attending school, with a high risk of recurrent infestation. Only the youngest household member attending school participated.

Interventions: Participants were treated and confirmed louse free. Randomly divided between octanediol or placebo sprays for 6 weeks then crossed-over to the other spray for 6 weeks. Parents applied the sprays at least twice each week or more frequently if the hair was washed. Investigators monitored weekly for infestation and replenished supplies of spray.

Main outcome measure: The primary end point was time to first infestation.

Results: Analysis by intention to treat found 32 confirmed infestations in 20 participants, with 9 infested using both products. For analysis, two who dropped out were treated as though they had both been infested equally in each arm of the study. This resulted in 11 participants who were infested in both arms of the study and therefore on both treatments. In these 11 participants the time to first infestation showed a significant advantage to 1% octanediol ($p = 0.0129$). Per-protocol analysis showed only trends because the population included was not large enough to demonstrate significance.

Conclusion: Regular use of 1% octanediol spray in school aged children at high risk of head louse infestation was shown to provide a significant level of protection from infestation. It can therefore be concluded that this product is effective if applied regularly and thoroughly.

Registration: ISRCTN09524995

STRENGTHS AND LIMITATIONS OF THIS STUDY

- As a pragmatic study, the results are an indication of how the product could perform in consumer use
- The primary limitation of the study was that the risk for infestation of each participant was unknown
- The results demonstrate the inconsistency with which even motivated people might use the product
- The study was able to demonstrate a statistically viable outcome for the data

INTRODUCTION

Head louse infestation continues to be common and widespread despite recent development of treatment products that are not affected by resistance to insecticides. There are numerous treatment choices in European countries but, although effective for most users, some children are repeatedly infested. Sometimes this is because care givers are not successful when using the treatment but often recently treated children are quickly reinfested.

When discussed with concerned parents, apart from effective treatments, most people wish for a product that can protect children against infestation. Some have interpreted this as using a repellent. [1, 2] However, repellents, by their nature, are volatile and therefore not persistent on hair, which means they have limited longevity, especially if the application is not thorough. [2] Also, because lice crawl from one head to another rather than seek hosts, the chemicals designed to disrupt the host-seeking function in flying insects may have no activity against crawling lice. In any case, it is recognised that mosquito repellents have limitations of effectiveness so that users may suffer occasional bites. If similar failures occurred with lice, infestations could become established without being noticed.

In the past it was mistakenly believed that insecticides with a residual action could protect against reinfestation for several weeks. [3] This was probably effective for some people but residual effects were inconsistent were systematically leached by hair washing so that the level of insecticide quickly became sub-lethal for any lice moving onto the hair. [3-6] Inevitably lice

in contact with low levels of insecticide were selected for resistance to pyrethroid and malathion insecticides in the early 1990s. [7]

The alternative prevention strategy is regular use of a product that prevents lice from establishing an infestation rather than repelling them. This was never appropriate for conventional insecticides, although anecdote suggests it may have been widely practised but regular use of low doses of cosmetically acceptable, physically acting, chemicals that disrupt the cuticular lipids of lice should kill insects in contact with the treated hair and limit the risk of an infestation establishing. We know that 1,2-octanediol 5% is effective to eliminate an established head louse infestation. [8] We also observed, during pre-clinical studies of 1,2-octanediol, that 1% solutions were able to kill lice, albeit more slowly, and inhibit egg laying. This report describes a randomised, double-blind, cross-over, clinical investigation of a spray containing 1% 1,2-octandiol, which was developed as a preventive of this type, compared with placebo.

MATERIALS AND METHODS

Participants

We recruited participants in a similar way to previous investigations by local radio advertising and by writing to families who had participated in previous clinical trials and expressed a wish to participate in further research. Prospective participants were sent an information booklet and if, after reading, they wished to take part an appointment was made for an appropriate date to start the study.

Unlike other studies, only the youngest member of the family who was attending school was recruited to the study. Thus the minimum age was 4 years and the maximum 16 years. Other members of the household were not included so they could act as potential sources of infestation for participants.

Everyone joining was conducted through a standardised consent/assent procedure and then assessed for presence of head lice using a plastic head louse detection comb (PDC, KSL Consulting, Denmark). This was mainly to provide information about the person's current risk status, because everyone was treated to ensure all participants started free from infestation. Other household members who were infested at this time were offered treatment to reduce the risk of an immediate reinfestation pressure on the index member.

All participants gave baseline data on age, gender, and hair characteristics as well as information on current medications and medical history. All treatments and assessments were conducted in participants' homes. There was no payment for participation.

Eligibility and inclusion criteria were being of appropriate age, as described above; being at risk of reinfestation based on previous individual and family history; and being willing to participate for the estimated 14 weeks of the study. Exclusion criteria were a history of allergy or sensitivity to components of the test product or placebo; of long term scalp disorders, such as impetigo or psoriasis; pregnancy or breast feeding; and participation in other clinical studies within 1 month prior to entry.

Ethics

Ethical approval in was granted by the National Research Ethics Service Committee North East – Northern & Yorkshire, Reference 12/NE/0253. A Clinical Trial Notification was also made to the Medicines and Healthcare Products Regulatory Agency in the UK, Reference CI/2012/0032. Parents provided written consent for the participating child. Participants also provided written assent. Each participant's General Practitioner was informed of their taking part.

The study was conducted in conformity with the principles of the Declaration of Helsinki and the ICH Guidelines and European Standard for Good Clinical Practice (GCP).

Study medications

This was a randomised, double-blind, cross-over study of a 1% 1,2-octanediol in a hair conditioning base (Hedrin Protect & Go, Thornton & Ross Ltd, UK). It was supplied in a 100mL trigger spray HDPE plastic bottles, used like a leave-in detangler conditioning spray, applied twice weekly to washed and towel dried hair. More frequent applications were permitted. The placebo comparator was superficially identical. Both required shaking before application and had a warning to avoid spraying onto the face, to prevent eye irritation.

At enrolment, and at cross-over between using the different treatment sprays, we provided treatment to all participants to eliminate any lice already present. For this we used dimeticone 4% liquid gel (Hedrin Once liquid gel, Thornton & Ross, UK) applied for 15 minutes before washing, with a repeat treatment after 7 days. We used the same product to treat infestations of

participants and household members acquired during the course of the study. Treatments were applied by investigators.

At the beginning of the study an instruction sheet was supplied to the parent/carer(s) for use with the sprays. At weekly intervals an investigator visited each family to check the participant for lice using a detection comb, supply a new bottle of spray, and return the used bottle to the study centre for weighing to determine the quantity used.

Definition of infestation

We expected that some lice would be found while using the preventive spray because it was possible that participants may have picked up lice at school during the afternoon prior to the visit. Therefore, no action was taken on first finding of lice unless there were five or more large lice (adult and third stage nymphs) or there were any small nymphs (first and second stage nymphs) present. Either of these was evidence that an infestation had been present for some time. Young nymphs would only be present if eggs had been laid on the head and most reinfestation events start with fewer than five adult or third stage nymphal lice. If lice of any stage were discovered on two consecutive visits this was considered primary evidence of an ongoing infestation. When infestation was confirmed it was treated using two applications a week apart of dimeticone 4% liquid gel and any lice discovered fixed into the case record using clear tape as confirmation.

Objectives

The study objective was to demonstrate that with regular use 1% octanediol spray could protect against head lice establishing an infestation by killing any lice that crawled onto the treated hair. Unlike a repellent, we recognised that lice would not be inhibited from crawling onto the head but that the product should, if it was applied correctly, be effective to limit the risk of an infestation becoming established for people using it.

Outcomes

The primary outcome measure was the time to first infestation, identified using systematic detection combing over the whole head. Secondary endpoints were whether infestations occurred at any time while using the product and the safety of the spray in use.

Sample size

This study was designed to detect superiority of 1% octanediol product compared with a placebo. The study was of an unusual type for clinical investigations because, unlike most clinical investigations, the participants in this study did not already have a treatable condition. The aim to prevent a treatable condition was also unlike other "preventive" studies, e.g. vaccine trials, in that those are normally long-term population studies engaging large numbers of participants with a quite small potential for detectable failure overall.

We proposed a cross-over design because it allowed smaller numbers of participants to be involved and allowing each participant to act as his/her own control. Developing the design was difficult because the risk factors for each individual are unknown so randomisation alone may not wholly address any disparity in infestation risk due to social and family circumstances,

especially in a relatively small study cohort. Consequently, self-controlling for each individual was an attractive option to avoid any skew resulting from these unknown factors.

The primary analysis, based on time-to-onset of first infestation, was considered a more powerful method of detecting differences between the 1% octanediol and the placebo than a simpler approach based on whether or not a participant gets an infestation.

The sample size calculations by the statistical consultant were based on 10,000 simulations of cross-over studies using a range of defined study sizes, setting the power to detect a difference significant at the 95% confidence level, and then estimating the minimum sample size to obtain 80% or 90% power. For the risk of infestation we looked at the experience of participants in previous studies of between 3 and 5 instances of reinfestation per year, estimated to be equivalent to a rate per person per week of about 6% to 10%. From this we expected a reduction of risk between 60% and 70% when using the active spray. Consequently, we selected a sample size of 68 participants based on assumed weekly infestation rates of 6% for placebo and 2% for octanediol, based on the estimated sample size for 80% power of 64 plus allowance for drop out. These were equivalent to weekly rates of survival from infestation of 94% for placebo and 98% for octanediol, or 6 week survival rates of 69.0% and 88.6%. This sample size gave expectation of 19.8 possible infestations for placebo and 7.8 for octanediol over the course of the study.

Randomisation – Allocation concealment

The randomised treatment allocation code was generated using the free online randomisation service at http://www.randomization.com/, seed number 26438 created on 10th October 2012.

Treatment allocation was made in 8 balanced blocks of 10 treatments, with one spare block randomised in case replacements were required.

The treatment allocations bore the anonymous identification of the product to be used and the instructions for application. The product identification/instruction sheets were sealed in opaque sequentially numbered envelopes with the participant number taken from the randomisation schedule. This study operated a cross-over design with each participant acting as their own control so all participants used both preparations during the course of the study. The product codes were not broken until after the completion of data collection, entry of data into the study database, and database lock.

Statistical analysis

Analyses testing for differences between the treatments accounted for the cross-over design and were based on within-participant differences between effectiveness of 1% octanediol compared with the placebo during the respective six-week treatment periods. Primary data management and analyses were performed by PN Lee Statistics and Computing Ltd in collaboration with the investigators. Binary data were analysed using the McNemar test and counts and ranked data using the Wilcoxon signed rank test for paired data. We analysed participants overall and separately in each randomisation arm, according to which treatment they received first.

For the primary outcome, the time to the first confirmed infestation, we used a seven point ranking to score the participants:

1 = infestation first confirmed at the first-follow-up assessment

2 = infestation first occurred at the second follow-up assessment

....

6 = infestation first occurred at the sixth follow-up assessment

7 = no infestation confirmed in the six assessments

Other endpoint analyses included whether infestation occurred at any time, how many infestations occurred during each 6 weeks treatment period, and the number and types of adverse events.

For the primary outcome, we used Kaplan-Meier curves to illustrate the time pattern of survival of the participants from infestation either when using 1% octanediol or when using placebo. We did not test differences between the treatments for significance using the log-rank test since, because the two curves were non-independent being based on the same participants.

We performed analyses on both the intention to treat (ITT) and per-protocol (PP) groups. We anticipated some drop outs, mostly during the second 6 week period of treatment. For analysis of drop out we assumed that an infestation had occurred the first week a follow up was not possible. Where this happened in the first treatment period, so there were no data for the second period, we assumed that the same response occurred in both 6 week periods.

We also analysed baseline characteristics to compare participants according to which product they were randomised to receive first. These data were compared using Fisher's exact test for binary data and the Mann-Whitney U test for counts and ranked variables.

RESULTS

Participant flow

We recruited 64 prospective participants but one of those became lost to follow up after only one pre-study treatment using dimeticone 4% liquid gel. As this individual had not entered the investigative treatment phase we considered that they had not actually commenced participation and should be eliminated from the analyses, leaving 63 enrolled participants in the ITT population, 34 given octanediol followed by placebo and 29 given placebo followed by octanediol. All participants were recruited from the area around Cambridge, UK. The majority were recruited between 22nd October and 16th November 2012. All participants had completed both arms of the study by mid-March 2013. Of those recruited, two participants failed to complete the study, one dropped out and one was lost to follow up.

Twenty participants were so inconsistent in product use we excluded from the PP population for protocol deviations. Reasons for exclusion could be classified into five types summarised in Figure 1: 6 participants accidentally used seven bottles of the first study treatment and five bottles of the second study treatment, instead of six bottles for each group; 2 were given rescue treatments at the wrong time; 1 was lost to follow up and 1 dropped out; 2 people could not be assessed within the agreed time window on three occasions. Some of these were also found to be

in a group that did not apply the products on a regular basis. Altogether 16 participants failed to apply the treatments correctly within agreed protocol limits. Fourteen of these (6 when using octanediol and 8 when using placebo) failed to use any spray during one or more weeks. Where the spray was only applied once in a given week, when it should have been applied at least twice, were considered minor protocol deviations. However, repeated inconsistency in use was considered a major deviation so, for the analyses, 2 people were excluded from the PP population because they applied spray only once during a week on three or more occasions.

These participants were included in the ITT analyses but were excluded from the PP analysis.

Baseline data

Of the 63 participants in the investigation phase, 50 (79.4%) were female, and 18 (28.6%) were aged 10 years or over, with the remainder aged 4 to 9 years. There was no significant difference between randomisation groups in age and sex and no significant difference in household size, number of members checked for lice in the household, or numbers of people found to have lice at baseline (Table 1). Of household members diagnosed with lice but not enrolled in the study, only one declined treatment to eliminate lice. Similarly, there were no differences between randomisation groups in hair length, degree of curl, or hair type. However, there was a significant ($p < 0.05$) difference in hair thickness, with participants allocated octanediol followed by placebo having thicker hair (52.9% thick, 32.4% medium, 14.7% fine) than those allocated placebo followed by octanediol (24.1% thick, 41.4% medium, 34.5% fine) but, as this was only one of a wide range of variables studied, it was not inconsistent with chance. Fourteen (22.2%) participants stated they averaged fewer than two hair washes per week. The percentage was

higher for participants allocated placebo followed by octanediol (34.5%) than for octanediol followed by placebo (11.8%). This difference was nearly significant ($0.05 < p < 0.1$). Five (7.9%) of the participants dyed their hair, with no difference seen between the randomisation groups. At enrolment, before treatment to eliminate lice, existing infestation was reported as "None" in 21 (33.3%), "Light" in 20 (31.7%), "Moderate" in 12 (19.0%), and "Heavy" in 10 (15.9%). There were no significant differences between randomisation groups and analyses did not suggest any major failure of randomisation.

Table 1. Demographic characteristics of the study population measured at baseline

Statistic	Octanediol then Placebo	Placebo then Octanediol	Total	P
Number of participants	34	29	63	
Mean age (years)	8.12	7.72	7.94	NS
% age 1-9	70.59	72.41	71.43	
% males	20.59	20.69	20.63	NS
Mean number living in household	4.44	4.69	4.56	NS
Mean number checked for lice	2.50	2.66	2.57	NS
Mean number with lice in household	1.38	1.14	1.27	NS
Hair length score [a]	3.38	3.34	3.37	NS
% with hair below shoulders	61.76	55.17	58.73	
Hair thickness score [b]	2.38	1.90	2.16	< 0.05
% with hair thick	52.94	24.14	39.68	
Degree of curl score [c]	1.62	1.34	1.49	NS
% with straight hair	58.82	75.86	66.67	
Mean hair type score [d]	1.97	2.10	2.03	NS
% with hair normal	97.06	89.66	93.65	
% with “continuous” or “constant” head lice, or with >10 infestations in the last year	35.29	44.83	39.68	NS
% washing hair less than twice per week	11.76	34.48	22.22	< 0.1
% using hair dye	5.88	10.34	7.94	NS
Mean infestation level [e]	1.29	1.03	1.17	NS

[a] Scoring 1 = closely cropped, 2 = above ears, 3 = ears to shoulders and 4 = below shoulders

[b] Scoring 1 = fine, 2 = medium, 3 = thick

[c] Scoring 1 = straight, 2 = wavy, 3 = slight curl, 4 = tight curl

[d] Scoring 1 = dry, 2 = normal, 3 = greasy

[e] Scoring 0 = none, 1 = light, 2 = moderate, 3 = heavy

Outcomes

All participants indicated that they were at risk of infestation and 42 (66.7%) had an existing infestation at the time of first examination. The remainder stated that they had recently or regularly experienced infestation and anticipated that they were likely to be exposed to further infestation. Of the 63 participants in the ITT population, all but two completed the study. One dropped out, and the other was lost to follow-up.

At each of the 12 weeks of the follow up, the assessor noted whether:

1. There were any live lice present
2. Lice were found at previous assessment but no action was taken
3. There were more than five lice
4. Any stage 1 or stage 2 nymphs were present

If an assessor found there were any live lice present ("**1**") and, if at the same time, any of "**2**", "**3**", or "**4**" also applied, this was considered to be an active infestation, the lice were collected and fixed into the case record book, and the participant treated to eliminate infestation. The numbers of each development stage, and the total numbers of lice were recorded after examination in the laboratory.

More lice were found during every week when placebo was used compared with the number found when using octanediol (Table 2, Figure 2). However, this difference was only found to be significant ($p < 0.05$) for the mean number of stage 2 nymphs at weeks 1 and 6 and almost significant ($0.05 < p < 0.1$) for mean number of stage 1 nymphs at weeks 4 and 6.

Intention to Treat Population

We found a total of 32 confirmed infestations in 20 participants, which broke down as 12 people (19.0%) infested when using octanediol and 17 people (27.0%) when using placebo, three people using placebo caught lice on two separate occasions (Table 2, Figure 2). Infestations occurred in 3 participants when using octanediol but not placebo, in 8 participants when using placebo but not octanediol, and in 9 participants when using both, to which, for analysis purposes, were added the two participants who dropped out who were each treated as though they had both been infested at the same point whilst using both treatments, making a total of 11 people with infestations using both treatments. In this group, the infestation occurred earlier with placebo than with octanediol in 7 participants, earlier with octanediol than placebo in just one, and in another the infestations occurred after the same time interval on both treatments (Table 2). The two who did not complete their participation were assigned the same score for both treatments.

This analysis of primary outcome, based on time to first confirmed infestation, showed a significant advantage ($p = 0.0129$) to 1% octanediol.

Including those who were only infested while using one treatment, there were 15 participants who did better while using octanediol (i.e. either they were only infested while using placebo or else they were infested earlier using placebo) compared with 4 who did better with placebo (Table 2). This difference is illustrated in Figure 3, the Kaplan-Meier plot of the proportions surviving free from confirmed infestation by week of participation in the study.

The comparison of rate of confirmed infestations, based on the 8 people infested only while using placebo, versus the three infested only while using octanediol, did not show a significant difference ($p = 0.2266$). Mean numbers of confirmed infestations were higher with placebo than with octanediol, 0.45 vs. 0.31. This difference was almost significant ($p = 0.0880$).

Table 2. Numbers of lice recovered from infested participants according to the week of receiving each spray treatment

	Number of lice recovered											
Treatment	**1% octanediol treatment period**						**Placebo treatment period**					
Week number	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**
Participant												
001			4					3				2
003							3					
007								2	6	5		
008												1
010							3					1
011									14			
015			3									
023			2						2	4		
031							3					
032			4									39
033						4					3	
037					5		3		5			
043										2	1	10
045					1							
046						4						
049						5					9	5
051					12					1	3	
054									4	4	4	5
055						1	1					
061						1			3	2		
Total lice	**0**	**0**	**13**	**0**	**18**	**15**	**13**	**5**	**34**	**18**	**20**	**63**

Per Protocol Population

After making allowance for various non-compliance issues, 26 participants were eliminated from the ITT population to leave 37 in the per-protocol analysis. Twenty-three of these were randomised to receive octanediol first. No significant differences were seen between treatments for any of the three outcomes considered, even at $p < 0.1$. However, the pattern was similar to that seen in the ITT population, with:

- A higher frequency of confirmed infestations using placebo (24.3%) than with octanediol (16.2%).
- A higher mean number of confirmed infestations using placebo (0.32) than octanediol (0.16).
- A shorter time to first infestation, with the mean scores 6.11 for placebo and 6.62 for octanediol.

The Kaplan-Meier comparison plot is shown in Figure 4.

Analyses of the rates of infestation, taking into account the various demographic characteristics, showed no significant difference between the two treatments.

Product use

Measurements of spray use were based on the bottle weights. The average use per bottle was 17.35ml for the octanediol spray and 18.90ml for the placebo. For octanediol average usage varied from 2.33ml to 62.08ml and for placebo from 1.43ml to 66.32ml in each week. These quantities were partly influenced by the number of applications given, with a few participants applying the spray daily. However, the quantity used per atomisation apparently varied greatly

and several people were less than accurate in the information they provided, either in the reported number of spray applications or in a few cases whether they had used the bottle at all.

Adverse events

There were no serious adverse events, and no adverse events that were considered probably related to treatment. The majority of adverse experiences were common childhood ailments and minor accidents to be expected in any population of this age range over a moderately prolonged observation period. There were two adverse events considered possibly related to treatment while using 1% octanediol. The first, a rash of moderate severity, required concomitant medication and was resolved in 5 days. The other, application site erythema, was mild, required no action, and resolved the same day.

DISCUSSION

We have conducted the first investigation of a non-repellent product intended to prevent head lice from establishing an infestation. We found that with regular use there was a significant ($p = 0.0129$) difference in time to first infestation when using 1% 1,2-octanediol spray compared with using placebo. There were also non-significant trends for a reduced risk of contracting an infestation and for lower numbers of lice surviving if users did become infested.

There are no data on incidence of head louse infestation from any source yet prior to commencement we needed to make estimates of the number of infestation exposures likely to occur during the study period. We made an estimate of the underlying weekly probabilities of

infestation in school children based on sales of pediculicides, adjusted for age group at risk, repetition of treatment, overall population, and local population sizes. The indicated risk, based on the school-aged population in general, suggested we could expect an infestation rate in the study group of approximately 0.31 cases per week, meaning for a 12 week study we could expect only around 4 cases to arise. Such a rate was clearly unsatisfactory and would not allow us to detect a difference between the two treatments. However, because we planned to primarily recruit from a population known to have experienced repeated infestations, and using data relating to when those people had contracted lice after study treatments, we found we could expect a risk of about 3-5 infestations per year per individual, i.e. a risk of about 3.6-4 possible reinfestation contacts per week for the whole group. However, we could not predict how many of these contacts would result in infestations. In practice we could not measure the number of "possible" infestation events, although we did observe and treat infestations in relatives throughout the study. The result was 32 confirmed infestations, an average of 2.67 each week, in addition to observed lice that failed to establish an infestation, close to our risk estimate.

We expected some infestations, either because people did not apply sufficient octanediol or else because it was applied inconsistently. It was also possible that more than five lice could transfer at one time so if they were seen before the treatment had time to take effect it could be mistakenly diagnosed as an infestation. This was most likely in participants with siblings contracting lice regularly, such as those participants who acquired infestations when using both the octanediol spray as well as the placebo. Consequently, the primary end point was determined around the time to first infestation rather than whether an infestation occurred at all and meant that clear analyses could only be performed on that smaller group of participants experiencing

infestations in both arms of the study. Despite this limitation on numbers, the outcomes provided a clear distinction between the treatments with a high level of significance ($p = 0.0129$).

Unlike repellents, 1% 1,2-octanediol is non-volatile but we do not know how effective it remains between hair washes, which is why the study required a minimum of two equally spaced applications each week. Octanediol is partially water soluble, and certainly surfactant soluble, at the dose rates applied so shampooing would remove it, so regular reapplication was necessary to maintain the protective effect. Our results show this regimen is effective, and would probably have been more effective if participants had applied more product and more consistently throughout the treatment period. In this respect, more thorough (or more frequent) applications may be appropriate at times of outbreaks of infestation in the local or school communities.

Many families have long wished for a preventive preparation. They may monitor and treat their own children but these efforts have been undermined by friends and neighbours who are less assiduous in their efforts or do not attempt to eliminate lice at all. We have found that 1% octanediol spray can prevent lice from establishing and delay onset of infestation when exposure is common. However, although all the carers professed to be concerned about lice the level of inconsistency of use suggests that relatively few will truly benefit from such a product unless they are prepared to invest the effort to use it properly. Nevertheless, if a high proportion of households in a community were to use a preventive it is possible that the background level of infestation could be reduced to the point where transmission becomes rare compared with when controlled by therapeutic agents alone. One approach to answering this question would be to conduct a study in which a whole community is provided with the protection spray, rather than

relatively isolated individuals, over a period of some months and the impact on infestation evaluated.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Therapeutic interventions have not reduced the prevalence of head louse infestation in the UK despite extensive use of products not affected by insecticide resistance.
- Many families struggle to manage problems with reinfestation on a regular basis.
- There is no evidence that prevention of infestation can be achieved using repellent chemicals

WHAT THIS STUDY ADDS

- This study indicates that a product designed to help prevent establishment of a head louse infestation can be effective with regular use.
- Over a six weeks period of twice weekly use of 1% 1,2-octanediol spray there was significantly ($p = 0.0129$) more effective to reduce the risk of infestation, measured by time to first infestation, compared with placebo.
- When using 1,2-octanediol participants experienced fewer infestations at lower intensity than when using placebo.

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Contributors: IFB and ERB were responsible for conception and design of the study. All authors were involved in data collection and management. IFB performed some of the statistical analyses. IFB was responsible for drafting and revising the manuscript. All authors approved the final version of the manuscript. IFB is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that this study was conducted by them as employees of Insect Research & Development Limited (IRD) on a commercial basis on behalf of Thornton & Ross Ltd.; IRD is a contract research organisation and has had various financial relationships, some of which are covered by confidential disclosure agreements, with numerous commercial entities that might have an interest in the submitted work during the previous three years; the individual authors have no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Ethical approval in was granted by the National Research Ethics Service Committee North East – Northern & Yorkshire, Reference 12/NE/0253. Written informed consent was obtained for all participants.

Data sharing: Participant level data are available from the corresponding author at ian@insectresearch.com. Participant consent was not obtained for data sharing but the presented data are anonymised and risk of identification is low.

Transparency declaration: The lead author (IFB) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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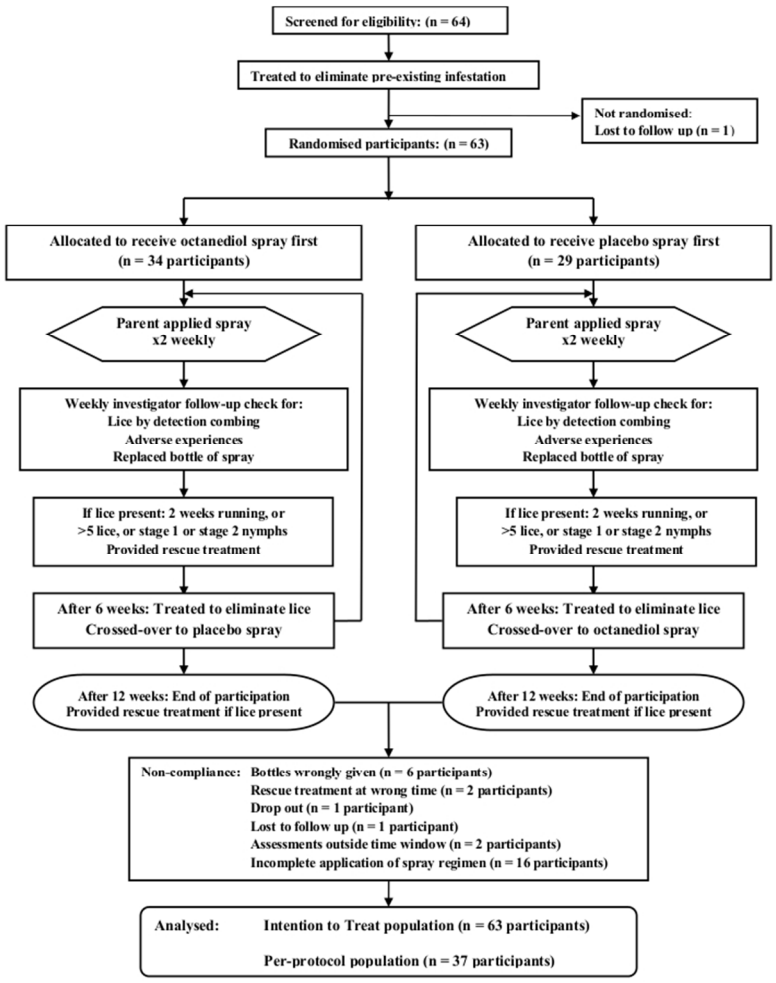
FIGURE LEGENDS

Figure 1. Flowchart of participants through the study

Figure 2. Relative number of infestations and numbers of lice recovered between the two treatments in the Intention to treat population

Figure 3. Kaplan-Meier plot of time to infestation Intention to treat population (A = active, B=placebo)

Figure 4. Kaplan-Meier plot of time to infestation Per-Protocol population (A=active, B=placebo)



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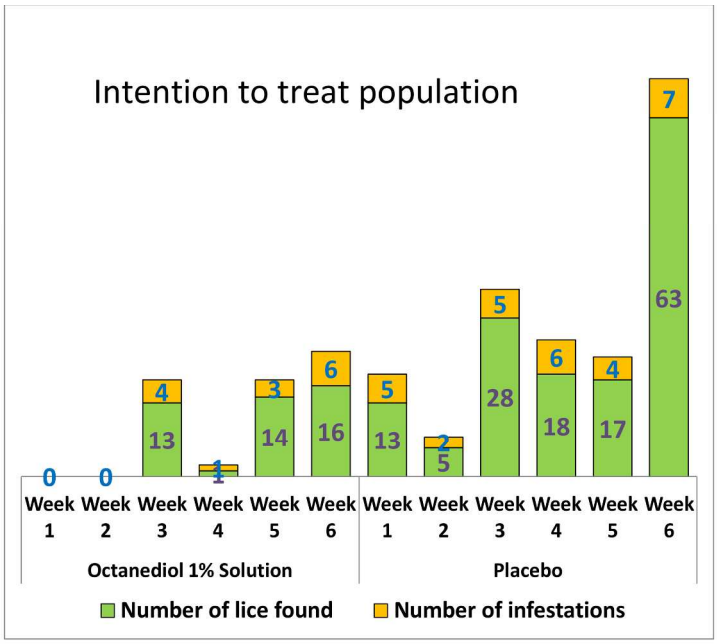

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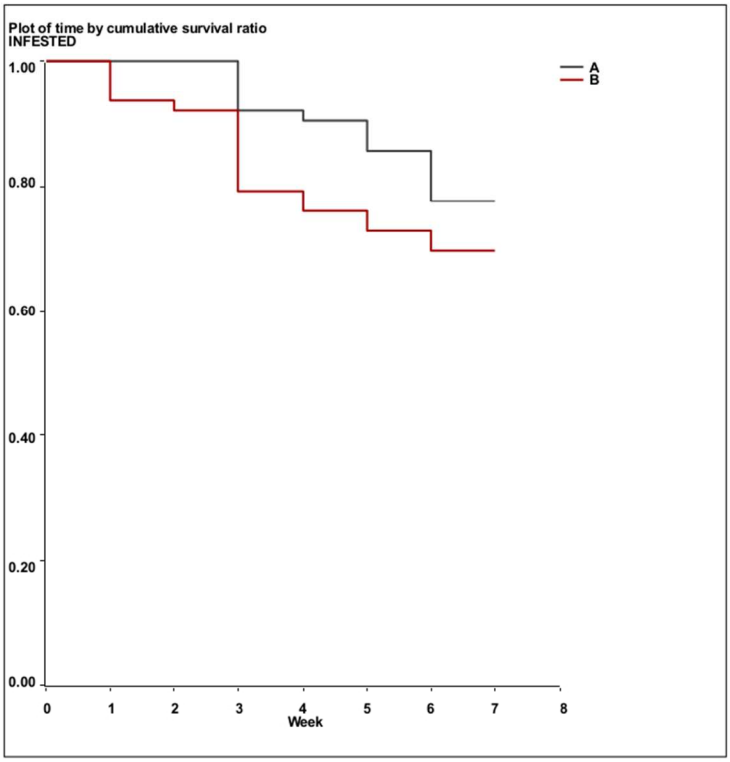

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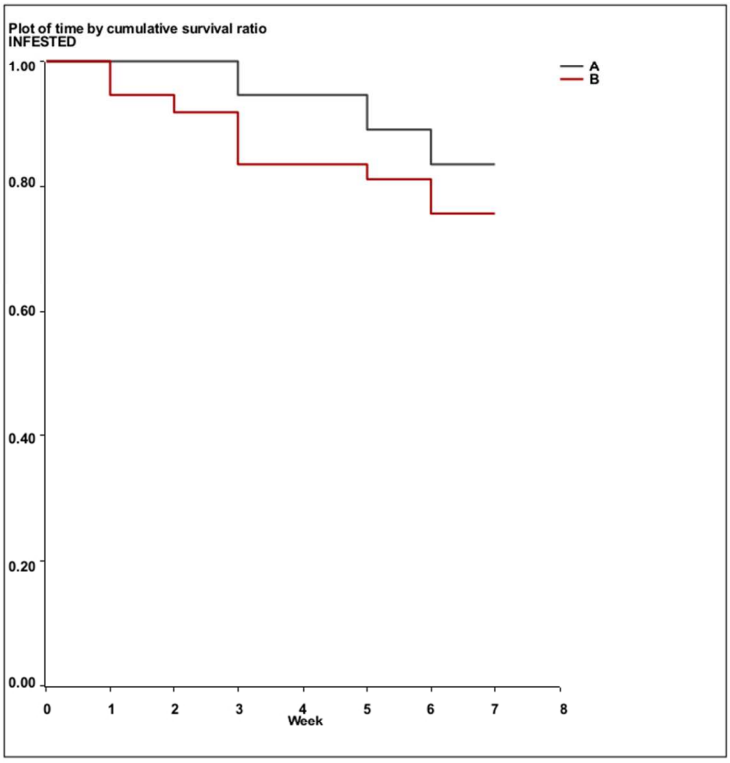

215x279mm (100 x 100 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	5, 6
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7, 8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	9, 10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10, 11
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10, 11
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	11
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10, 11
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7, 11

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11-13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11-13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	13-14
	13b	For each group, losses and exclusions after randomisation, together with reasons	13-14
Recruitment	14a	Dates defining the periods of recruitment and follow-up	13
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	16
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	14, 17-21
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	17-21
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	17-21
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	22
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	22-24
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	22-24
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	24-25
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Supplementary file
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	26

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Prevention of head louse infestation: A randomised, double-blind, cross-over study of a novel concept product, 1% 1,2-octandiol spray versus placebo.

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Primary Subject Heading:	Public health
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Prevention of head louse infestation: A randomised, double-blind, cross-over study of a novel concept product, 1% 1,2-octandiol spray versus placebo.

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Keywords: head lice, pediculosis, preventive, 1,2-octanediol,

Word count: 4509

ABSTRACT

Objectives: To determine whether regular use of a spray containing 1,2-octanediol 1%, which has been shown to inhibit survival of head lice, is able to work as a preventive against establishment of new infestations.

Setting: Randomised, double blind, cross-over, community study in Cambridgeshire, UK.

Participants: 63 male and female schoolchildren aged 4-16 judged to have a high risk of recurrent infestation. Only the youngest member of a household attending school participated.

Interventions: Participants were treated to eliminate lice, randomised between 1% octanediol or placebo sprays for 6 weeks then crossed-over to the other spray for 6 weeks. Parents applied sprays at least twice weekly or more frequently if the hair was washed. Investigators monitored weekly for infestation and replenished supplies of spray

Primary and secondary outcome measures: The primary end point was the time taken until the first infestation event occurred. The secondary measure was safety of the product in regular use.

Results: ITT analysis found a total of 32 confirmed infestations in 20 participants, with 9 of these infested while using both products. In these 9 participants the time to first infestation showed a significant advantage to 1% octanediol ($p = 0.0129$). Per-protocol analysis showed only trends because the population included was not large enough to demonstrate significance. There were no serious adverse events and only two adverse events possibly related to treatment, one case of transient erythema and another of a rash that resolved after 5 days.

Conclusions: Routine use of 1% octanediol spray provided a significant level of protection from infestation. It was concluded that this product is effective if applied regularly and thoroughly.

Trial registration: ISRCTN09524995

STRENGTHS AND LIMITATIONS OF THIS STUDY

- As a pragmatic study, the results are an indication of how the product could perform in consumer use
- The primary limitation of the study was that the risk for infestation of each participant was unknown
- The results demonstrate the inconsistency with which even motivated people might use the product
- The study was able to demonstrate a statistically viable outcome for the data

INTRODUCTION

Head louse infestation continues to be common and widespread despite recent development of treatment products that are not affected by resistance to insecticides. There are numerous treatment choices in European countries but, although effective for most users, some children are repeatedly infested. Sometimes this is because care givers are not successful when using the treatment but often recently treated children are quickly reinfested.

When discussed with concerned parents, apart from effective treatments, most people wish for a product that can protect children against infestation. Some have interpreted this as using a repellent. [1, 2] However, repellents, by their nature, are volatile and therefore not persistent on hair, which means they have limited longevity, especially if the application is not thorough. [2] Also, because lice crawl from one head to another rather than seek hosts, the chemicals designed to disrupt the host-seeking function in flying insects may have no activity against crawling lice. In any case, it is recognised that mosquito repellents have limitations of effectiveness so that users may suffer occasional bites. If similar failures occurred with lice, infestations could become established without being noticed.

In the past it was mistakenly believed that insecticides with a residual action could protect against reinfestation for several weeks. [3] This was probably effective for some people but residual effects were inconsistent were systematically leached by hair washing so that the level of insecticide quickly became sub-lethal for any lice moving onto the hair. [3-6] Inevitably lice

in contact with low levels of insecticide were selected for resistance to pyrethroid and malathion insecticides in the early 1990s. [7]

The alternative prevention strategy is regular use of a product that prevents lice from establishing an infestation rather than repelling them. This was never appropriate for conventional insecticides, although anecdote suggests it may have been widely practised but regular use of low doses of cosmetically acceptable, physically acting, chemicals that disrupt the cuticular lipids of lice should kill insects in contact with the treated hair and limit the risk of an infestation establishing. We know that 1,2-octanediol 5% is effective to eliminate an established head louse infestation. [8] We also observed, during pre-clinical studies of 1,2-octanediol, that 1% solutions were able to kill lice, albeit more slowly, and inhibit egg laying. This report describes a randomised, double-blind, cross-over, clinical investigation of a spray containing 1% 1,2-octandiol, which was developed as a preventive of this type, compared with placebo.

MATERIALS AND METHODS

Participants

We recruited participants in a similar way to previous investigations by local radio advertising and by writing to families who had participated in previous clinical trials and expressed a wish to participate in further research. Prospective participants were sent an information booklet and if, after reading, they wished to take part an appointment was made for an appropriate date to start the study.

Unlike other studies, only the youngest member of the family who was attending school was recruited to the study. Thus the minimum age was 4 years and the maximum 16 years. Other members of the household were not included so they could act as potential sources of infestation for participants.

Everyone joining was conducted through a standardised consent/assent procedure and then assessed for presence of head lice using a plastic head louse detection comb (PDC, KSL Consulting, Denmark). This was mainly to provide information about the person's current risk status, because everyone was treated to ensure all participants started free from infestation. Other household members who were infested at this time were offered treatment to reduce the risk of an immediate reinfestation pressure on the index member.

All participants gave baseline data on age, gender, and hair characteristics as well as information on current medications and medical history. All treatments and assessments were conducted in participants' homes. There was no payment for participation.

Eligibility and inclusion criteria were being of appropriate age, as described above; being at risk of reinfestation based on previous individual and family history; and being willing to participate for the estimated 14 weeks of the study. Exclusion criteria were a history of allergy or sensitivity to components of the test product or placebo; of long term scalp disorders, such as impetigo or psoriasis; pregnancy or breast feeding; and participation in other clinical studies within 1 month prior to entry.

Ethics

Ethical approval in was granted by the National Research Ethics Service Committee North East – Northern & Yorkshire, Reference 12/NE/0253. A Clinical Trial Notification was also made to the Medicines and Healthcare Products Regulatory Agency in the UK, Reference CI/2012/0032. Parents provided written consent for the participating child. Participants also provided written assent. Each participant's General Practitioner was informed of their taking part.

The study was conducted in conformity with the principles of the Declaration of Helsinki and the ICH Guidelines and European Standard for Good Clinical Practice (GCP).

Study medications

This was a randomised, double-blind, cross-over study of a 1% 1,2-octanediol in a hair conditioning base (Hedrin Protect & Go, Thornton & Ross Ltd, UK). It was supplied in a 100mL trigger spray HDPE plastic bottles, used like a leave-in detangler conditioning spray, applied twice weekly to washed and towel dried hair. More frequent applications were permitted during the 6 weeks period of use, for example if the participant washed their hair more regularly. The placebo comparator was superficially identical and applied in the same way and at the same rate. Both required shaking before application and had a warning to avoid spraying onto the face, to prevent eye irritation.

At enrolment, and at cross-over between using the different treatment sprays, we provided treatment to all participants to eliminate any lice already present, even if none were detected. For this we used dimeticone 4% liquid gel (Hedrin Once liquid gel, Thornton & Ross, UK)

applied for 15 minutes before washing, with a repeat treatment after 7 days, which was not strictly necessary due to the high level of efficacy exhibited by the product [9] but the second application was a requirement of approval for the study by the MHRA assessor. We used the same product to treat infestations of participants and household members acquired during the course of the study. Participants who were found to have contracted an infestation at any point were not withdrawn. Treatments were applied by investigators. Participants who had been infested continued to use their designated spray during the period between applications of dimeticone liquid gel because the therapeutic product is non-residual and thus conferred no protective effect between treatments.

At the beginning of the study an instruction sheet was supplied to the parent/carer(s) for use with the sprays. At weekly intervals an investigator visited each family to check the participant for lice using a detection comb, supply a new bottle of spray, and return the used bottle to the study centre for weighing to determine the quantity used.

Definition of infestation

We expected that some lice would be found while using the preventive spray because it was possible that participants may have picked up lice at school during the afternoon prior to the visit. Therefore, no action was taken on first finding of lice unless there were five or more large lice (adult and third stage nymphs) or there were any small nymphs (first and second stage nymphs) present. Either of these was evidence that an infestation had been present for some time. Young nymphs would only be present if eggs had been laid on the head and most reinfestation events start with fewer than five adult or third stage nymphal lice. If lice of any

stage were discovered on two consecutive visits this was considered primary evidence of an ongoing infestation. When infestation was confirmed it was treated using two applications a week apart of dimeticone 4% liquid gel and any lice discovered fixed into the case record using clear tape as confirmation.

At each of the 12 weeks of the follow up, the assessor noted whether:

1. There were any live lice present
2. Lice were found at previous assessment but no action was taken
3. There were more than five lice
4. Any stage 1 or stage 2 nymphs were present

If an assessor found there were any live lice present ("**1**") and, if at the same time, any of "**2**", "**3**", or "**4**" also applied, this was considered to be an active infestation, the lice were collected and fixed into the case record book, and the participant treated to eliminate infestation. The numbers of each development stage, and the total numbers of lice were recorded after examination in the laboratory.

Objectives

The study objective was to demonstrate that with regular use 1% octanediol spray could protect against head lice establishing an infestation by killing any lice that crawled onto the treated hair. Unlike a repellent, we recognised that lice would not be inhibited from crawling onto the head but that the product should, if it was applied correctly, be effective to limit the risk of an infestation becoming established for people using it.

Outcomes

The primary outcome measure was the time to first infestation, identified using systematic detection combing over the whole head. Secondary endpoints were whether infestations occurred at any time while using the product and the safety of the spray in use.

Sample size

This study was designed to detect superiority of 1% octanediol product compared with a placebo. The study was of an unusual type for clinical investigations because, unlike most clinical investigations, the participants in this study did not already have a treatable condition. The aim to prevent a treatable condition was also unlike other "preventive" studies, e.g. vaccine trials, in that those are normally long-term population studies engaging large numbers of participants with a quite small potential for detectable failure overall.

We proposed a cross-over design because it allowed smaller numbers of participants to be involved and allowing each participant to act as his/her own control. Developing the design was difficult because the risk factors for each individual are unknown so randomisation alone may not wholly address any disparity in infestation risk due to social and family circumstances, especially in a relatively small study cohort. Consequently, self-controlling for each individual was an attractive option to avoid any skew resulting from these unknown factors.

The primary analysis, based on time-to-onset of first infestation, was considered a more powerful method of detecting differences between the 1% octanediol and the placebo than a simpler approach based on whether or not a participant gets an infestation.

The sample size calculations by the statistical consultant were based on 10,000 simulations of cross-over studies using a range of defined study sizes, setting the power to detect a difference significant at the 95% confidence level, and then estimating the minimum sample size to obtain 80% or 90% power. For the risk of infestation we looked at the experience of participants in previous studies of between 3 and 5 instances of reinfestation per year, estimated to be equivalent to a rate per person per week of about 6% to 10%. From this we expected a reduction of risk between 60% and 70% when using the active spray. Consequently, we selected a sample size of 68 participants based on assumed weekly infestation rates of 6% for placebo and 2% for octanediol, based on the estimated sample size for 80% power of 64 plus allowance for drop out. These were equivalent to weekly rates of survival from infestation of 94% for placebo and 98% for octanediol, or 6 week survival rates of 69.0% and 88.6%. This sample size gave expectation of 19.8 possible infestations for placebo and 7.8 for octanediol over the course of the study.

Randomisation – Allocation concealment

The randomised treatment allocation code was generated using the free online randomisation service at http://www.randomization.com/, seed number 26438 created on 10th October 2012. Treatment allocation was made in 8 balanced blocks of 10 treatments, with one spare block randomised in case replacements were required.

The treatment allocations bore the anonymous identification of the product to be used and the instructions for application. The product identification/instruction sheets were sealed in opaque sequentially numbered envelopes with the participant number taken from the randomisation schedule. This study operated a cross-over design with each participant acting as their own control so all participants used both preparations during the course of the study. The product codes were not broken until after the completion of data collection, entry of data into the study database, and database lock.

Statistical analysis

Analyses testing for differences between the treatments accounted for the cross-over design and were based on within-participant differences between effectiveness of 1% octanediol compared with the placebo during the respective six-week treatment periods. Primary data management and analyses were performed by PN Lee Statistics and Computing Ltd in collaboration with the investigators. Binary data were analysed using the McNemar test and counts and ranked data using the Wilcoxon signed rank test for paired data. We analysed participants overall and separately in each randomisation arm, according to which treatment they received first.

For the primary outcome, the time to the first confirmed infestation, we used a seven point ranking to score the participants:

1 = infestation first confirmed at the first-follow-up assessment

2 = infestation first occurred at the second follow-up assessment

....

6 = infestation first occurred at the sixth follow-up assessment

7 = no infestation confirmed in the six assessments

Other endpoint analyses included whether infestation occurred at any time, how many new infestations occurred during each 6 weeks treatment period, and the number and types of adverse events.

For the primary outcome, we used Kaplan-Meier curves to illustrate the time pattern of survival of the participants from infestation either when using 1% octanediol or when using placebo. We did not test differences between the treatments for significance using the log-rank test because the two curves were non-independent being based on the same participants.

We performed analyses on both the intention to treat (ITT) and per-protocol (PP) groups. Prior to commencement we anticipated some drop outs, mostly during the second 6 week period of treatment. In order to address this problem, if it arose, we planned analyses to allow for drop out by making an assumption that this would be due to infestation. Thus for analysis of drop out we assumed that an infestation had occurred the first week a follow up was not possible. If this were to happen in the first treatment period, so there were no data for the second period, we made the assumption that the same response would have occurred in both 6 week periods. However, based on previous experience in this community, we also anticipated that drop out, were it to occur, would arise at a very low rate that would not require censoring or other specific measures to address the issue in the analyses.

We also analysed baseline characteristics to compare participants according to which product they were randomised to receive first. These data were compared using Fisher's exact test for binary data and the Mann-Whitney U test for counts and ranked variables.

RESULTS

Participant flow

We recruited 64 prospective participants but one of those became lost to follow up after only one pre-study treatment using dimeticone 4% liquid gel. As this individual had not entered the investigative treatment phase we considered that they had not actually commenced participation and should be eliminated from the analyses, leaving 63 enrolled participants in the ITT population, 34 given octanediol followed by placebo and 29 given placebo followed by octanediol. All participants were recruited from the area around Cambridge, UK. The majority were recruited between 22nd October and 16th November 2012. All participants had completed both arms of the study by mid-March 2013. Of those recruited, two participants failed to complete the study, one dropped out and one was lost to follow up.

Twenty participants were so inconsistent in product use we excluded from the PP population for protocol deviations. Reasons for exclusion could be classified into five types summarised in Figure 1: 6 participants accidentally used seven bottles of the first study treatment and five bottles of the second study treatment, instead of six bottles for each group; 2 were given rescue treatments at the wrong time; 1 was lost to follow up and 1 dropped out; 2 people could not be assessed within the agreed time window on three occasions. Some of these were also found to be

in a group that did not apply the products on a regular basis. Altogether 16 participants failed to apply the treatments correctly within agreed protocol limits. Fourteen of these (6 when using octanediol and 8 when using placebo) failed to use any spray during one or more weeks. Where the spray was only applied once in a given week, when it should have been applied at least twice, were considered minor protocol deviations. However, repeated inconsistency in use was considered a major deviation so, for the analyses, 2 people were excluded from the PP population because they applied spray only once during a week on three or more occasions.

These participants were included in the ITT analyses but were excluded from the PP analysis.

Baseline data

Of the 63 participants in the investigation phase, 50 (79.4%) were female, and 18 (28.6%) were aged 10 years or over, with the remainder aged 4 to 9 years. There was no significant difference between randomisation groups in age and sex and no significant difference in household size, number of members checked for lice in the household, or numbers of people found to have lice at baseline (Table 1). Of household members diagnosed with lice but not enrolled in the study, only one declined treatment to eliminate lice. Similarly, there were no differences between randomisation groups in hair length, degree of curl, or hair type. However, there was a significant ($p < 0.05$) difference in hair thickness, with participants allocated octanediol followed by placebo having thicker hair (52.9% thick, 32.4% medium, 14.7% fine) than those allocated placebo followed by octanediol (24.1% thick, 41.4% medium, 34.5% fine) but, as this was only one of a wide range of variables studied, it was not inconsistent with chance. Fourteen (22.2%) participants stated they averaged fewer than two hair washes per week. The percentage was

higher for participants allocated placebo followed by octanediol (34.5%) than for octanediol followed by placebo (11.8%). This difference was nearly significant ($0.05 < p < 0.1$). Five (7.9%) of the participants dyed their hair, with no difference seen between the randomisation groups. At enrolment, before treatment to eliminate lice, existing infestation was reported as "None" in 21 (33.3%), "Light" in 20 (31.7%), "Moderate" in 12 (19.0%), and "Heavy" in 10 (15.9%). There were no significant differences between randomisation groups and analyses did not suggest any major failure of randomisation.

Table 1. Demographic characteristics of the study population measured at baseline

Statistic	Octanediol then Placebo	Placebo then Octanediol	Total	P
Number of participants	34	29	63	
Mean age (years)	8.12	7.72	7.94	NS
% age 1-9	70.59	72.41	71.43	
% males	20.59	20.69	20.63	NS
Mean number living in household	4.44	4.69	4.56	NS
Mean number checked for lice	2.50	2.66	2.57	NS
Mean number with lice in household	1.38	1.14	1.27	NS
Hair length score [a]	3.38	3.34	3.37	NS
% with hair below shoulders	61.76	55.17	58.73	
Hair thickness score [b]	2.38	1.90	2.16	< 0.05
% with hair thick	52.94	24.14	39.68	
Degree of curl score [c]	1.62	1.34	1.49	NS
% with straight hair	58.82	75.86	66.67	
Mean hair type score [d]	1.97	2.10	2.03	NS
% with hair normal	97.06	89.66	93.65	
% with “continuous” or “constant” head lice, or with >10 infestations in the last year	35.29	44.83	39.68	NS
% washing hair less than twice per week	11.76	34.48	22.22	< 0.1
% using hair dye	5.88	10.34	7.94	NS
Mean infestation level [e]	1.29	1.03	1.17	NS

[a] Scoring 1 = closely cropped, 2 = above ears, 3 = ears to shoulders and 4 = below shoulders
[b] Scoring 1 = fine, 2 = medium, 3 = thick
[c] Scoring 1 = straight, 2 = wavy, 3 = slight curl, 4 = tight curl
[d] Scoring 1 = dry, 2 = normal, 3 = greasy
[e] Scoring 0 = none, 1 = light, 2 = moderate, 3 = heavy

Outcomes

All participants indicated that they were at risk of infestation and 42 (66.7%) had an existing infestation at the time of first examination. The remainder stated that they had recently or regularly experienced infestation and anticipated that they were likely to be exposed to further infestation. Of the 63 participants in the ITT population, all but two completed the study. One dropped out, and the other was lost to follow-up.

More lice were found during every week when placebo was used compared with the number found when using octanediol (Table 2, Figure 2). However, this difference was only found to be significant ($p < 0.05$) for the mean number of stage 2 nymphs at weeks 1 and 6 and almost significant ($0.05 < p < 0.1$) for mean number of stage 1 nymphs at weeks 4 and 6.

Intention to Treat Population

We found a total of 32 confirmed infestations in 20 participants, which broke down as 12 people (19.0%) infested when using octanediol and 17 people (27.0%) when using placebo, three people using placebo caught lice on two separate occasions (Table 2, Figure 2). Infestations occurred in 3 participants when using octanediol but not placebo, in 8 participants when using placebo but not octanediol, and in 9 participants when using both. In this group, the infestation occurred earlier with placebo than with octanediol in 7 participants, earlier with octanediol than placebo in just one, and in another the infestations occurred after the same time interval on both treatments (Table 2).

This analysis of primary outcome, based on time to first confirmed infestation, showed a significant advantage (p = 0.0129) to 1% octanediol.

Including those who were only infested while using one treatment, there were 15 participants who did better while using octanediol (i.e. either they were only infested while using placebo or else they were infested earlier using placebo) compared with 4 who did better with placebo (Table 2). This difference is illustrated in Figure 3, the Kaplan-Meier plot of the proportions surviving free from confirmed infestation by week of participation in the study.

The comparison of rate of confirmed infestations, based on the 8 people infested only while using placebo, versus the three infested only while using octanediol, did not show a significant difference (p = 0.2266). Overall 19.7% of participants were found to be infested while using octanediol compared with 27.9% of those using placebo. Among these we found a significant (p = 0.0453) advantage to 1% octanediol in relation to the primary outcome of time to first infestation in the group randomised to receive placebo first then octanediol. We found no advantage in the group receiving octanediol followed by placebo.

Table 2. Numbers of lice recovered from infested participants according to the week of receiving each spray treatment

	Number of lice recovered											
Treatment	**1% octanediol treatment period**						**Placebo treatment period**					
Week number	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**
Participant												
001			4					3				2
003							3					
007								2	6	5		
008												1
010							3					1
011									14			
015			3									
023			2						2	4		
031							3					
032			4									39
033						4					3	
037					5		3		5			
043										2	1	10
045					1							
046						4						
049						5					9	5
051					12					1	3	
054									4	4	4	5
055						1	1					
061						1			3	2		
No. infestations	0	0	4	0	3	5	5	2	6	6	5	7
Cumulative no. infestations	0	0	4	4	7	12	5	7	13	19	24	31
Total lice	**0**	**0**	**13**	**0**	**18**	**15**	**13**	**5**	**34**	**18**	**20**	**63**

Per Protocol Population

After making allowance for various non-compliance issues, 26 participants were eliminated from the ITT population to leave 37 in the per-protocol analysis. Twenty-three of these were randomised to receive octanediol first. No significant differences were seen between treatments for any of the three outcomes considered, even at $p < 0.1$. However, the pattern was similar to that seen in the ITT population, with:

- A higher frequency of confirmed infestations using placebo (24.3%) than with octanediol (16.2%).
- A shorter time to first infestation, with the mean scores 6.11 for placebo and 6.62 for octanediol.

The Kaplan-Meier comparison plot is shown in Figure 4.

Analyses of the rates of infestation, taking into account the various demographic characteristics, showed no significant difference between the two treatments.

Product use

Measurements of spray use were based on the bottle weights. The average use per bottle was 17.35ml for the octanediol spray and 18.90ml for the placebo. For octanediol average usage varied from 2.33ml to 62.08ml and for placebo from 1.43ml to 66.32ml in each week. These quantities were partly influenced by the number of applications given, with a few participants applying the spray daily. However, the quantity used per atomisation apparently varied greatly and several people were less than accurate in the information they provided, either in the reported number of spray applications or in a few cases whether they had used the bottle at all.

Adverse events

There were no serious adverse events, and no adverse events that were considered probably related to treatment. The majority of adverse experiences were common childhood ailments and minor accidents to be expected in any population of this age range over a moderately prolonged observation period. There were two adverse events considered possibly related to treatment while using 1% octanediol. The first, a rash of moderate severity, required concomitant medication and was resolved in 5 days. The other, application site erythema, was mild, required no action, and resolved the same day.

DISCUSSION

We have conducted the first investigation of a non-repellent product intended to prevent head lice from establishing an infestation. We found that with regular use there was a significant ($p = 0.0129$) difference in time to first infestation when using 1% 1,2-octanediol spray compared with using placebo. There were also non-significant trends for a reduced risk of contracting an infestation and for lower numbers of lice surviving if users did become infested.

There are no data on incidence of head louse infestation from any source yet prior to commencement we needed to make estimates of the number of infestation exposures likely to occur during the study period. We made an estimate of the underlying weekly probabilities of infestation in school children based on sales of pediculicides, adjusted for age group at risk, repetition of treatment, overall population, and local population sizes. The indicated risk, based

on the school-aged population in general, suggested we could expect an infestation rate in the study group of approximately 0.31 cases per week, meaning for a 12 week study we could expect only around 4 cases to arise. Such a rate was clearly unsatisfactory and would not allow us to detect a difference between the two treatments. However, because we planned to primarily recruit from a population known to have experienced repeated infestations, and using data relating to when those people had contracted lice after study treatments, we found we could expect a risk of about 3-5 infestations per year per individual, i.e. a risk of about 3.6-4 possible reinfestation contacts per week for the whole group. However, we could not predict how many of these contacts would result in infestations. In practice we could not measure the number of "possible" infestation events, although we did observe and treat infestations in relatives throughout the study. The result was 32 confirmed infestations, an average of 2.67 each week, in addition to observed lice that failed to establish an infestation, close to our risk estimate.

We expected some infestations, either because people did not apply sufficient octanediol or else because it was applied inconsistently. It was also possible that more than five lice could transfer at one time so if they were seen before the treatment had time to take effect it could be mistakenly diagnosed as an infestation. This was most likely in participants with siblings contracting lice regularly, such as those participants who acquired infestations when using both the octanediol spray as well as the placebo. Consequently, the primary end point was determined around the time to first infestation rather than whether an infestation occurred at all and meant that clear analyses could only be performed on that smaller group of participants experiencing infestations in both arms of the study. Despite this limitation on numbers, the outcomes provided a clear distinction between the treatments with a high level of significance ($p = 0.0129$).

Unlike repellents, 1% 1,2-octanediol is non-volatile but we do not know how effective it remains between hair washes, which is why the study required a minimum of two equally spaced applications each week. Octanediol is partially water soluble, and certainly surfactant soluble, at the dose rates applied so shampooing would remove it, so regular reapplication was necessary to maintain the protective effect. Our results show this regimen is effective, and would probably have been more effective if participants had applied more product and more consistently throughout the treatment period. In this respect, more thorough (or more frequent) applications may be appropriate at times of outbreaks of infestation in the local or school communities.

Many families have long wished for a preventive preparation. They may monitor and treat their own children but these efforts have been undermined by friends and neighbours who are less assiduous in their efforts or do not attempt to eliminate lice at all. We have found that 1% octanediol spray can prevent lice from establishing and delay onset of infestation when exposure is common. However, although all the carers professed to be concerned about lice the level of inconsistency of use suggests that relatively few will truly benefit from such a product unless they are prepared to invest the effort to use it properly. Nevertheless, if a high proportion of households in a community were to use a preventive it is possible that the background level of infestation could be reduced to the point where transmission becomes rare compared with when controlled by therapeutic agents alone. One approach to answering this question would be to conduct a study in which a whole community is provided with the protection spray, rather than relatively isolated individuals, over a period of some months and the impact on infestation evaluated.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Therapeutic interventions have not reduced the prevalence of head louse infestation in the UK despite extensive use of products not affected by insecticide resistance.
- Many families struggle to manage problems with reinfestation on a regular basis.
- There is no evidence that prevention of infestation can be achieved using repellent chemicals

WHAT THIS STUDY ADDS

- This study indicates that a product designed to help prevent establishment of a head louse infestation can be effective with regular use.
- Over a six weeks period of twice weekly use of 1% 1,2-octanediol spray there was significantly ($p = 0.0129$) more effective to reduce the risk of infestation, measured by time to first infestation, compared with placebo.
- When using 1,2-octanediol participants experienced fewer infestations at lower intensity than when using placebo.

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Contributors: IFB and ERB were responsible for conception and design of the study. All authors were involved in data collection and management. IFB performed some of the statistical analyses. IFB was responsible for drafting and revising the manuscript. All authors approved the final version of the manuscript. IFB is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that this study was conducted by them as employees of Insect Research & Development Limited (IRD) on a commercial basis on behalf of Thornton & Ross Ltd.; IRD is a contract research organisation and has had various financial relationships, some of which are covered by confidential disclosure agreements, with numerous

commercial entities that might have an interest in the submitted work during the previous three years; the individual authors have no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Ethical approval in was granted by the National Research Ethics Service Committee North East – Northern & Yorkshire, Reference 12/NE/0253. Written informed consent was obtained for all participants.

Data sharing: Participant level data are available from the corresponding author at ian@insectresearch.com. Participant consent was not obtained for data sharing but the presented data are anonymised and risk of identification is low.

Transparency declaration: The lead author (IFB) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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FIGURE LEGENDS

Figure 1. Flowchart of participants through the study

Figure 2. Relative number of infestations and numbers of lice recovered between the two treatments in the Intention to treat population

Figure 3. Kaplan-Meier plot of time to infestation Intention to Treat population (A = active, B=placebo)

Figure 4. Kaplan-Meier plot of time to infestation Per-Protocol population (A=active, B=placebo)

Prevention of head louse infestation: A randomised, double-blind, cross-over study of a novel concept product, 1% 1,2-octandiol spray versus placebo.

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ABSTRACT

Objectives: To determine whether regular use of a spray containing 1,2-octanediol 1%, which has been shown to inhibit survival of head lice, is able to work as a preventive against establishment of new infestations.

Setting: Randomised, double blind, cross-over, community study in Cambridgeshire, UK.

Participants: 63 male and female schoolchildren aged 4-16 judged to have a high risk of recurrent infestation. Only the youngest member of a household attending school participated.

Interventions: Participants were treated to eliminate lice, randomised between 1% octanediol or placebo sprays for 6 weeks then crossed-over to the other spray for 6 weeks. Parents applied sprays at least twice weekly or more frequently if the hair was washed. Investigators monitored weekly for infestation and replenished supplies of spray

Primary and secondary outcome measures: The primary end point was the time taken until the first infestation event occurred. The secondary measure was safety of the product in regular use.

Results: ITT analysis found a total of 32 confirmed infestations in 20 participants, with 9 of these infested while using both products. In these 9 participants the time to first infestation showed a significant advantage to 1% octanediol ($p = 0.0129$). Per-protocol analysis showed only trends because the population included was not large enough to demonstrate significance. There were no serious adverse events and only two adverse events possibly related to treatment, one case of transient erythema and another of a rash that resolved after 5 days.

Conclusions: Routine use of 1% octanediol spray provided a significant level of protection from infestation. It was concluded that this product is effective if applied regularly and thoroughly.

Trial registration: ISRCTN09524995

STRENGTHS AND LIMITATIONS OF THIS STUDY

- As a pragmatic study, the results are an indication of how the product could perform in consumer use
- The primary limitation of the study was that the risk for infestation of each participant was unknown
- The results demonstrate the inconsistency with which even motivated people might use the product
- The study was able to demonstrate a statistically viable outcome for the data

INTRODUCTION

Head louse infestation continues to be common and widespread despite recent development of treatment products that are not affected by resistance to insecticides. There are numerous treatment choices in European countries but, although effective for most users, some children are repeatedly infested. Sometimes this is because care givers are not successful when using the treatment but often recently treated children are quickly reinfested.

When discussed with concerned parents, apart from effective treatments, most people wish for a product that can protect children against infestation. Some have interpreted this as using a repellent. [1, 2] However, repellents, by their nature, are volatile and therefore not persistent on hair, which means they have limited longevity, especially if the application is not thorough. [2] Also, because lice crawl from one head to another rather than seek hosts, the chemicals designed to disrupt the host-seeking function in flying insects may have no activity against crawling lice. In any case, it is recognised that mosquito repellents have limitations of effectiveness so that users may suffer occasional bites. If similar failures occurred with lice, infestations could become established without being noticed.

In the past it was mistakenly believed that insecticides with a residual action could protect against reinfestation for several weeks. [3] This was probably effective for some people but residual effects were inconsistent were systematically leached by hair washing so that the level of insecticide quickly became sub-lethal for any lice moving onto the hair. [3-6] Inevitably lice

in contact with low levels of insecticide were selected for resistance to pyrethroid and malathion insecticides in the early 1990s. [7]

The alternative prevention strategy is regular use of a product that prevents lice from establishing an infestation rather than repelling them. This was never appropriate for conventional insecticides, although anecdote suggests it may have been widely practised but regular use of low doses of cosmetically acceptable, physically acting, chemicals that disrupt the cuticular lipids of lice should kill insects in contact with the treated hair and limit the risk of an infestation establishing. We know that 1,2-octanediol 5% is effective to eliminate an established head louse infestation. [8] We also observed, during pre-clinical studies of 1,2-octanediol, that 1% solutions were able to kill lice, albeit more slowly, and inhibit egg laying. This report describes a randomised, double-blind, cross-over, clinical investigation of a spray containing 1% 1,2-octandiol, which was developed as a preventive of this type, compared with placebo.

MATERIALS AND METHODS

Participants

We recruited participants in a similar way to previous investigations by local radio advertising and by writing to families who had participated in previous clinical trials and expressed a wish to participate in further research. Prospective participants were sent an information booklet and if, after reading, they wished to take part an appointment was made for an appropriate date to start the study.

Unlike other studies, only the youngest member of the family who was attending school was recruited to the study. Thus the minimum age was 4 years and the maximum 16 years. Other members of the household were not included so they could act as potential sources of infestation for participants.

Everyone joining was conducted through a standardised consent/assent procedure and then assessed for presence of head lice using a plastic head louse detection comb (PDC, KSL Consulting, Denmark). This was mainly to provide information about the person's current risk status, because everyone was treated to ensure all participants started free from infestation. Other household members who were infested at this time were offered treatment to reduce the risk of an immediate reinfestation pressure on the index member.

All participants gave baseline data on age, gender, and hair characteristics as well as information on current medications and medical history. All treatments and assessments were conducted in participants' homes. There was no payment for participation.

Eligibility and inclusion criteria were being of appropriate age, as described above; being at risk of reinfestation based on previous individual and family history; and being willing to participate for the estimated 14 weeks of the study. Exclusion criteria were a history of allergy or sensitivity to components of the test product or placebo; of long term scalp disorders, such as impetigo or psoriasis; pregnancy or breast feeding; and participation in other clinical studies within 1 month prior to entry.

Ethics

Ethical approval in was granted by the National Research Ethics Service Committee North East – Northern & Yorkshire, Reference 12/NE/0253. A Clinical Trial Notification was also made to the Medicines and Healthcare Products Regulatory Agency in the UK, Reference CI/2012/0032. Parents provided written consent for the participating child. Participants also provided written assent. Each participant's General Practitioner was informed of their taking part.

The study was conducted in conformity with the principles of the Declaration of Helsinki and the ICH Guidelines and European Standard for Good Clinical Practice (GCP).

Study medications

This was a randomised, double-blind, cross-over study of a 1% 1,2-octanediol in a hair conditioning base (Hedrin Protect & Go, Thornton & Ross Ltd, UK). It was supplied in a 100mL trigger spray HDPE plastic bottles, used like a leave-in detangler conditioning spray, applied twice weekly to washed and towel dried hair. More frequent applications were permitted during the 6 weeks period of use, for example if the participant washed their hair more regularly. The placebo comparator was superficially identical and applied in the same way and at the same rate. Both required shaking before application and had a warning to avoid spraying onto the face, to prevent eye irritation.

At enrolment, and at cross-over between using the different treatment sprays, we provided treatment to all participants to eliminate any lice already present, even if none were detected. For this we used dimeticone 4% liquid gel (Hedrin Once liquid gel, Thornton & Ross, UK)

applied for 15 minutes before washing, with a repeat treatment after 7 days, which was not strictly necessary due to the high level of efficacy exhibited by the product [9] but the second application was a requirement of approval for the study by the MHRA assessor. We used the same product to treat infestations of participants and household members acquired during the course of the study. Participants who were found to have contracted an infestation at any point were not withdrawn. Treatments were applied by investigators. Participants who had been infested continued to use their designated spray during the period between applications of dimeticone liquid gel because the therapeutic product is non-residual and thus conferred no protective effect between treatments.

At the beginning of the study an instruction sheet was supplied to the parent/carer(s) for use with the sprays. At weekly intervals an investigator visited each family to check the participant for lice using a detection comb, supply a new bottle of spray, and return the used bottle to the study centre for weighing to determine the quantity used.

Definition of infestation

We expected that some lice would be found while using the preventive spray because it was possible that participants may have picked up lice at school during the afternoon prior to the visit. Therefore, no action was taken on first finding of lice unless there were five or more large lice (adult and third stage nymphs) or there were any small nymphs (first and second stage nymphs) present. Either of these was evidence that an infestation had been present for some time. Young nymphs would only be present if eggs had been laid on the head and most reinfestation events start with fewer than five adult or third stage nymphal lice. If lice of any

stage were discovered on two consecutive visits this was considered primary evidence of an ongoing infestation. When infestation was confirmed it was treated using two applications a week apart of dimeticone 4% liquid gel and any lice discovered fixed into the case record using clear tape as confirmation.

At each of the 12 weeks of the follow up, the assessor noted whether:

1. There were any live lice present

2. Lice were found at previous assessment but no action was taken

3. There were more than five lice

4. Any stage 1 or stage 2 nymphs were present

If an assessor found there were any live lice present ("**1**") and, if at the same time, any of "**2**", "**3**", or "**4**" also applied, this was considered to be an active infestation, the lice were collected and fixed into the case record book, and the participant treated to eliminate infestation. The numbers of each development stage, and the total numbers of lice were recorded after examination in the laboratory.

Objectives

The study objective was to demonstrate that with regular use 1% octanediol spray could protect against head lice establishing an infestation by killing any lice that crawled onto the treated hair. Unlike a repellent, we recognised that lice would not be inhibited from crawling onto the head but that the product should, if it was applied correctly, be effective to limit the risk of an infestation becoming established for people using it.

Outcomes

The primary outcome measure was the time to first infestation, identified using systematic detection combing over the whole head. Secondary endpoints were whether infestations occurred at any time while using the product and the safety of the spray in use.

Sample size

This study was designed to detect superiority of 1% octanediol product compared with a placebo. The study was of an unusual type for clinical investigations because, unlike most clinical investigations, the participants in this study did not already have a treatable condition. The aim to prevent a treatable condition was also unlike other "preventive" studies, e.g. vaccine trials, in that those are normally long-term population studies engaging large numbers of participants with a quite small potential for detectable failure overall.

We proposed a cross-over design because it allowed smaller numbers of participants to be involved and allowing each participant to act as his/her own control. Developing the design was difficult because the risk factors for each individual are unknown so randomisation alone may not wholly address any disparity in infestation risk due to social and family circumstances, especially in a relatively small study cohort. Consequently, self-controlling for each individual was an attractive option to avoid any skew resulting from these unknown factors.

The primary analysis, based on time-to-onset of first infestation, was considered a more powerful method of detecting differences between the 1% octanediol and the placebo than a simpler approach based on whether or not a participant gets an infestation.

The sample size calculations by the statistical consultant were based on 10,000 simulations of cross-over studies using a range of defined study sizes, setting the power to detect a difference significant at the 95% confidence level, and then estimating the minimum sample size to obtain 80% or 90% power. For the risk of infestation we looked at the experience of participants in previous studies of between 3 and 5 instances of reinfestation per year, estimated to be equivalent to a rate per person per week of about 6% to 10%. From this we expected a reduction of risk between 60% and 70% when using the active spray. Consequently, we selected a sample size of 68 participants based on assumed weekly infestation rates of 6% for placebo and 2% for octanediol, based on the estimated sample size for 80% power of 64 plus allowance for drop out. These were equivalent to weekly rates of survival from infestation of 94% for placebo and 98% for octanediol, or 6 week survival rates of 69.0% and 88.6%. This sample size gave expectation of 19.8 possible infestations for placebo and 7.8 for octanediol over the course of the study.

Randomisation – Allocation concealment

The randomised treatment allocation code was generated using the free online randomisation service at http://www.randomization.com/, seed number 26438 created on 10th October 2012. Treatment allocation was made in 8 balanced blocks of 10 treatments, with one spare block randomised in case replacements were required.

The treatment allocations bore the anonymous identification of the product to be used and the instructions for application. The product identification/instruction sheets were sealed in opaque sequentially numbered envelopes with the participant number taken from the randomisation schedule. This study operated a cross-over design with each participant acting as their own control so all participants used both preparations during the course of the study. The product codes were not broken until after the completion of data collection, entry of data into the study database, and database lock.

Statistical analysis

Analyses testing for differences between the treatments accounted for the cross-over design and were based on within-participant differences between effectiveness of 1% octanediol compared with the placebo during the respective six-week treatment periods. Primary data management and analyses were performed by PN Lee Statistics and Computing Ltd in collaboration with the investigators. Binary data were analysed using the McNemar test and counts and ranked data using the Wilcoxon signed rank test for paired data. We analysed participants overall and separately in each randomisation arm, according to which treatment they received first.

For the primary outcome, the time to the first confirmed infestation, we used a seven point ranking to score the participants:

1 = infestation first confirmed at the first-follow-up assessment

2 = infestation first occurred at the second follow-up assessment

....

6 = infestation first occurred at the sixth follow-up assessment

7 = no infestation confirmed in the six assessments

Other endpoint analyses included whether infestation occurred at any time, how many new infestations occurred during each 6 weeks treatment period, and the number and types of adverse events.

For the primary outcome, we used Kaplan-Meier curves to illustrate the time pattern of survival of the participants from infestation either when using 1% octanediol or when using placebo. We did not test differences between the treatments for significance using the log-rank test ~~since,~~ because the two curves were non-independent being based on the same participants.

We performed analyses on both the intention to treat (ITT) and per-protocol (PP) groups. ~~We~~ Prior to commencement we anticipated some drop outs, mostly during the second 6 week period of treatment. In order to address this problem, if it arose, we planned analyses to allow for drop out by making an assumption that this would be due to infestation. Thus ~~For~~ for analysis of drop out we assumed that an infestation had occurred the first week a follow up was not possible. ~~Where this happened~~If this were to happen in the first treatment period, so there were no data for the second period, we ~~assumed~~ made the assumption that the same response would have occurred in both 6 week periods. However, based on previous experience in this community, we also anticipated that drop out, were it to occur, would arise at a very low rate that would not require censoring or other specific measures to address the issue in the analyses.

We also analysed baseline characteristics to compare participants according to which product they were randomised to receive first. These data were compared using Fisher's exact test for binary data and the Mann-Whitney U test for counts and ranked variables.

RESULTS

Participant flow

We recruited 64 prospective participants but one of those became lost to follow up after only one pre-study treatment using dimeticone 4% liquid gel. As this individual had not entered the investigative treatment phase we considered that they had not actually commenced participation and should be eliminated from the analyses, leaving 63 enrolled participants in the ITT population, 34 given octanediol followed by placebo and 29 given placebo followed by octanediol. All participants were recruited from the area around Cambridge, UK. The majority were recruited between 22nd October and 16th November 2012. All participants had completed both arms of the study by mid-March 2013. Of those recruited, two participants failed to complete the study, one dropped out and one was lost to follow up.

Twenty participants were so inconsistent in product use we excluded from the PP population for protocol deviations. Reasons for exclusion could be classified into five types summarised in Figure 1: 6 participants accidentally used seven bottles of the first study treatment and five bottles of the second study treatment, instead of six bottles for each group; 2 were given rescue treatments at the wrong time; 1 was lost to follow up and 1 dropped out; 2 people could not be assessed within the agreed time window on three occasions. Some of these were also found to be

in a group that did not apply the products on a regular basis. Altogether 16 participants failed to apply the treatments correctly within agreed protocol limits. Fourteen of these (6 when using octanediol and 8 when using placebo) failed to use any spray during one or more weeks. Where the spray was only applied once in a given week, when it should have been applied at least twice, were considered minor protocol deviations. However, repeated inconsistency in use was considered a major deviation so, for the analyses, 2 people were excluded from the PP population because they applied spray only once during a week on three or more occasions.

These participants were included in the ITT analyses but were excluded from the PP analysis.

Baseline data

Of the 63 participants in the investigation phase, 50 (79.4%) were female, and 18 (28.6%) were aged 10 years or over, with the remainder aged 4 to 9 years. There was no significant difference between randomisation groups in age and sex and no significant difference in household size, number of members checked for lice in the household, or numbers of people found to have lice at baseline (Table 1). Of household members diagnosed with lice but not enrolled in the study, only one declined treatment to eliminate lice. Similarly, there were no differences between randomisation groups in hair length, degree of curl, or hair type. However, there was a significant ($p < 0.05$) difference in hair thickness, with participants allocated octanediol followed by placebo having thicker hair (52.9% thick, 32.4% medium, 14.7% fine) than those allocated placebo followed by octanediol (24.1% thick, 41.4% medium, 34.5% fine) but, as this was only one of a wide range of variables studied, it was not inconsistent with chance. Fourteen (22.2%) participants stated they averaged fewer than two hair washes per week. The percentage was

higher for participants allocated placebo followed by octanediol (34.5%) than for octanediol followed by placebo (11.8%). This difference was nearly significant ($0.05 < p < 0.1$). Five (7.9%) of the participants dyed their hair, with no difference seen between the randomisation groups. At enrolment, before treatment to eliminate lice, existing infestation was reported as "None" in 21 (33.3%), "Light" in 20 (31.7%), "Moderate" in 12 (19.0%), and "Heavy" in 10 (15.9%). There were no significant differences between randomisation groups and analyses did not suggest any major failure of randomisation.

Table 1. Demographic characteristics of the study population measured at baseline

Statistic	Octanediol then Placebo	Placebo then Octanediol	Total	P
Number of participants	34	29	63	
Mean age (years)	8.12	7.72	7.94	NS
% age 1-9	70.59	72.41	71.43	
% males	20.59	20.69	20.63	NS
Mean number living in household	4.44	4.69	4.56	NS
Mean number checked for lice	2.50	2.66	2.57	NS
Mean number with lice in household	1.38	1.14	1.27	NS
Hair length score [a]	3.38	3.34	3.37	NS
% with hair below shoulders	61.76	55.17	58.73	
Hair thickness score [b]	2.38	1.90	2.16	< 0.05
% with hair thick	52.94	24.14	39.68	
Degree of curl score [c]	1.62	1.34	1.49	NS
% with straight hair	58.82	75.86	66.67	
Mean hair type score [d]	1.97	2.10	2.03	NS
% with hair normal	97.06	89.66	93.65	
% with “continuous” or “constant” head lice, or with >10 infestations in the last year	35.29	44.83	39.68	NS
% washing hair less than twice per week	11.76	34.48	22.22	< 0.1
% using hair dye	5.88	10.34	7.94	NS
Mean infestation level [e]	1.29	1.03	1.17	NS

[a] Scoring 1 = closely cropped, 2 = above ears, 3 = ears to shoulders and 4 = below shoulders
[b] Scoring 1 = fine, 2 = medium, 3 = thick
[c] Scoring 1 = straight, 2 = wavy, 3 = slight curl, 4 = tight curl
[d] Scoring 1 = dry, 2 = normal, 3 = greasy
[e] Scoring 0 = none, 1 = light, 2 = moderate, 3 = heavy

Outcomes

All participants indicated that they were at risk of infestation and 42 (66.7%) had an existing infestation at the time of first examination. The remainder stated that they had recently or regularly experienced infestation and anticipated that they were likely to be exposed to further infestation. Of the 63 participants in the ITT population, all but two completed the study. One dropped out, and the other was lost to follow-up.

~~At each of the 12 weeks of the follow-up, the assessor noted whether:~~

~~**1.** There were any live lice present~~

~~**2.** Lice were found at previous assessment but no action was taken~~

~~**3**. There were more than five lice~~

~~**4.** Any stage 1 or stage 2 nymphs were present~~

~~If an assessor found there were any live lice present ("**1**") and, if at the same time, any of "**2**", "**3**", or "**4**" also applied, this was considered to be an active infestation, the lice were collected and fixed into the case record book, and the participant treated to eliminate infestation. The numbers of each development stage, and the total numbers of lice were recorded after examination in the laboratory.~~

More lice were found during every week when placebo was used compared with the number found when using octanediol (Table 2, Figure 2). However, this difference was only found to be significant ($p < 0.05$) for the mean number of stage 2 nymphs at weeks 1 and 6 and almost significant ($0.05 < p < 0.1$) for mean number of stage 1 nymphs at weeks 4 and 6.

Intention to Treat Population

We found a total of 32 confirmed infestations in 20 participants, which broke down as 12 people (19.0%) infested when using octanediol and 17 people (27.0%) when using placebo, three people using placebo caught lice on two separate occasions (Table 2, Figure 2). Infestations occurred in 3 participants when using octanediol but not placebo, in 8 participants when using placebo but not octanediol, and in 9 participants when using both~~, to which, for analysis purposes, were added the two participants who dropped out who were each treated as though they had both been infested at the same point whilst using both treatments, making a total of 11 people with infestations using both treatments~~. In this group, the infestation occurred earlier with placebo than with octanediol in 7 participants, earlier with octanediol than placebo in just one, and in another the infestations occurred after the same time interval on both treatments (Table 2). ~~The two who did not complete their participation were assigned the same score for both treatments.~~

This analysis of primary outcome, based on time to first confirmed infestation, showed a significant advantage ($p = 0.0129$) to 1% octanediol.

Including those who were only infested while using one treatment, there were 15 participants who did better while using octanediol (i.e. either they were only infested while using placebo or else they were infested earlier using placebo) compared with 4 who did better with placebo (Table 2). This difference is illustrated in Figure 3, the Kaplan-Meier plot of the proportions surviving free from confirmed infestation by week of participation in the study.

The comparison of rate of confirmed infestations, based on the 8 people infested only while using placebo, versus the three infested only while using octanediol, did not show a significant difference (p = 0.2266). ~~Mean numbers of confirmed infestations were higher with placebo than with octanediol, 0.45 vs. 0.31. This difference was almost significant (p = 0.0880).~~ Overall 19.7% of participants were found to be infested while using octanediol compared with 27.9% of those using placebo. Among these we found a significant (p = 0.0453) advantage to 1% octanediol in relation to the primary outcome of time to first infestation in the group randomised to receive placebo first then octanediol. We found no advantage in the group receiving octanediol followed by placebo.

Table 2. Numbers of lice recovered from infested participants according to the week of receiving each spray treatment

	Number of lice recovered											
Treatment	**1% octanediol treatment period**						**Placebo treatment period**					
Week number	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**
Participant												
001			4					3				2
003							3					
007								2	6	5		
008												1
010							3					1
011									14			
015			3									
023			2						2	4		
031							3					
032			4									39
033						4					3	
037					5		3		5			
043										2	1	10
045					1							
046						4						
049						5					9	5
051					12					1	3	
054									4	4	4	5
055						1	1					
061						1			3	2		
No. infestations	0	0	4	0	3	5	5	2	6	6	5	7
Cumulative no. infestations	0	0	4	4	7	12	5	7	13	19	24	31
Total lice	**0**	**0**	**13**	**0**	**18**	**15**	**13**	**5**	**34**	**18**	**20**	**63**

Per Protocol Population

After making allowance for various non-compliance issues, 26 participants were eliminated from the ITT population to leave 37 in the per-protocol analysis. Twenty-three of these were randomised to receive octanediol first. No significant differences were seen between treatments for any of the three outcomes considered, even at $p < 0.1$. However, the pattern was similar to that seen in the ITT population, with:

- A higher frequency of confirmed infestations using placebo (24.3%) than with octanediol (16.2%).
- ~~A higher mean number of confirmed infestations using placebo (0.32) than octanediol (0.16).~~
- A shorter time to first infestation, with the mean scores 6.11 for placebo and 6.62 for octanediol.

The Kaplan-Meier comparison plot is shown in Figure 4.

Analyses of the rates of infestation, taking into account the various demographic characteristics, showed no significant difference between the two treatments.

Product use

Measurements of spray use were based on the bottle weights. The average use per bottle was 17.35ml for the octanediol spray and 18.90ml for the placebo. For octanediol average usage varied from 2.33ml to 62.08ml and for placebo from 1.43ml to 66.32ml in each week. These quantities were partly influenced by the number of applications given, with a few participants applying the spray daily. However, the quantity used per atomisation apparently varied greatly

and several people were less than accurate in the information they provided, either in the reported number of spray applications or in a few cases whether they had used the bottle at all.

Adverse events

There were no serious adverse events, and no adverse events that were considered probably related to treatment. The majority of adverse experiences were common childhood ailments and minor accidents to be expected in any population of this age range over a moderately prolonged observation period. There were two adverse events considered possibly related to treatment while using 1% octanediol. The first, a rash of moderate severity, required concomitant medication and was resolved in 5 days. The other, application site erythema, was mild, required no action, and resolved the same day.

DISCUSSION

We have conducted the first investigation of a non-repellent product intended to prevent head lice from establishing an infestation. We found that with regular use there was a significant ($p = 0.0129$) difference in time to first infestation when using 1% 1,2-octanediol spray compared with using placebo. There were also non-significant trends for a reduced risk of contracting an infestation and for lower numbers of lice surviving if users did become infested.

There are no data on incidence of head louse infestation from any source yet prior to commencement we needed to make estimates of the number of infestation exposures likely to occur during the study period. We made an estimate of the underlying weekly probabilities of

infestation in school children based on sales of pediculicides, adjusted for age group at risk, repetition of treatment, overall population, and local population sizes. The indicated risk, based on the school-aged population in general, suggested we could expect an infestation rate in the study group of approximately 0.31 cases per week, meaning for a 12 week study we could expect only around 4 cases to arise. Such a rate was clearly unsatisfactory and would not allow us to detect a difference between the two treatments. However, because we planned to primarily recruit from a population known to have experienced repeated infestations, and using data relating to when those people had contracted lice after study treatments, we found we could expect a risk of about 3-5 infestations per year per individual, i.e. a risk of about 3.6-4 possible reinfestation contacts per week for the whole group. However, we could not predict how many of these contacts would result in infestations. In practice we could not measure the number of "possible" infestation events, although we did observe and treat infestations in relatives throughout the study. The result was 32 confirmed infestations, an average of 2.67 each week, in addition to observed lice that failed to establish an infestation, close to our risk estimate.

We expected some infestations, either because people did not apply sufficient octanediol or else because it was applied inconsistently. It was also possible that more than five lice could transfer at one time so if they were seen before the treatment had time to take effect it could be mistakenly diagnosed as an infestation. This was most likely in participants with siblings contracting lice regularly, such as those participants who acquired infestations when using both the octanediol spray as well as the placebo. Consequently, the primary end point was determined around the time to first infestation rather than whether an infestation occurred at all and meant that clear analyses could only be performed on that smaller group of participants experiencing

infestations in both arms of the study. Despite this limitation on numbers, the outcomes provided a clear distinction between the treatments with a high level of significance ($p = 0.0129$).

Unlike repellents, 1% 1,2-octanediol is non-volatile but we do not know how effective it remains between hair washes, which is why the study required a minimum of two equally spaced applications each week. Octanediol is partially water soluble, and certainly surfactant soluble, at the dose rates applied so shampooing would remove it, so regular reapplication was necessary to maintain the protective effect. Our results show this regimen is effective, and would probably have been more effective if participants had applied more product and more consistently throughout the treatment period. In this respect, more thorough (or more frequent) applications may be appropriate at times of outbreaks of infestation in the local or school communities.

Many families have long wished for a preventive preparation. They may monitor and treat their own children but these efforts have been undermined by friends and neighbours who are less assiduous in their efforts or do not attempt to eliminate lice at all. We have found that 1% octanediol spray can prevent lice from establishing and delay onset of infestation when exposure is common. However, although all the carers professed to be concerned about lice the level of inconsistency of use suggests that relatively few will truly benefit from such a product unless they are prepared to invest the effort to use it properly. Nevertheless, if a high proportion of households in a community were to use a preventive it is possible that the background level of infestation could be reduced to the point where transmission becomes rare compared with when controlled by therapeutic agents alone. One approach to answering this question would be to conduct a study in which a whole community is provided with the protection spray, rather than

relatively isolated individuals, over a period of some months and the impact on infestation evaluated.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Therapeutic interventions have not reduced the prevalence of head louse infestation in the UK despite extensive use of products not affected by insecticide resistance.
- Many families struggle to manage problems with reinfestation on a regular basis.
- There is no evidence that prevention of infestation can be achieved using repellent chemicals

WHAT THIS STUDY ADDS

- This study indicates that a product designed to help prevent establishment of a head louse infestation can be effective with regular use.
- Over a six weeks period of twice weekly use of 1% 1,2-octanediol spray there was significantly ($p = 0.0129$) more effective to reduce the risk of infestation, measured by time to first infestation, compared with placebo.
- When using 1,2-octanediol participants experienced fewer infestations at lower intensity than when using placebo.

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Contributors: IFB and ERB were responsible for conception and design of the study. All authors were involved in data collection and management. IFB performed some of the statistical analyses. IFB was responsible for drafting and revising the manuscript. All authors approved the final version of the manuscript. IFB is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that this study was conducted by them as employees of Insect Research & Development Limited (IRD) on a commercial basis on behalf of Thornton & Ross Ltd.; IRD is a contract research organisation and has had various financial relationships, some of which are covered by confidential disclosure agreements, with numerous commercial entities that might have an interest in the submitted work during the previous three years; the individual authors have no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Ethical approval in was granted by the National Research Ethics Service Committee North East – Northern & Yorkshire, Reference 12/NE/0253. Written informed consent was obtained for all participants.

Data sharing: Participant level data are available from the corresponding author at ian@insectresearch.com. Participant consent was not obtained for data sharing but the presented data are anonymised and risk of identification is low.

Transparency declaration: The lead author (IFB) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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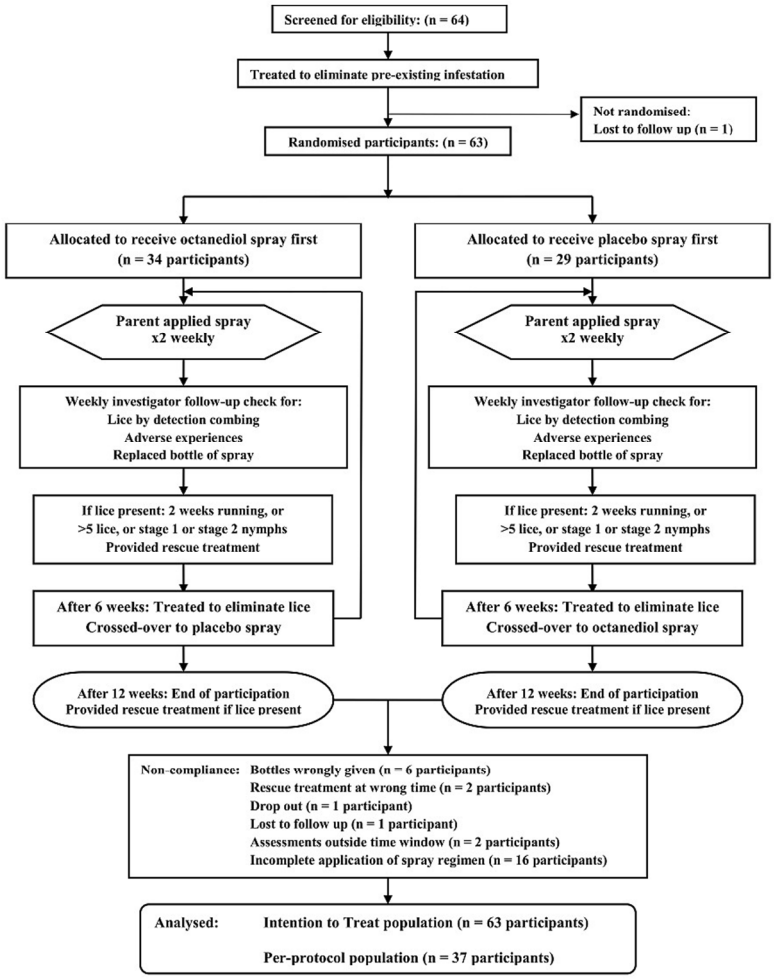
FIGURE LEGENDS

Figure 1. Flowchart of participants through the study

Figure 2. Relative number of infestations and numbers of lice recovered between the two treatments in the Intention to treat population

Figure 3. Kaplan-Meier plot of time to infestation Intention to treat population (A = active, B=placebo)

Figure 4. Kaplan-Meier plot of time to infestation Per-Protocol population (A=active, B=placebo)



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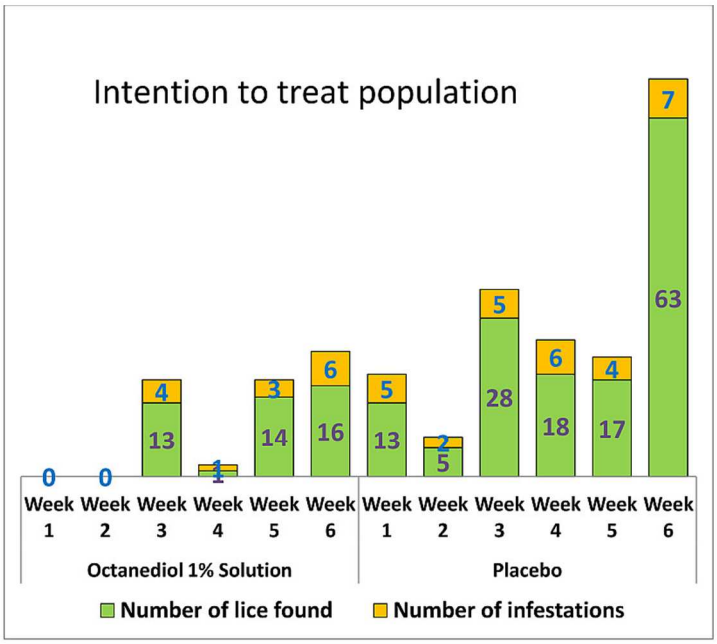

Relative number of infestations and numbers of lice recovered between the two treatments in the Intention to treat population
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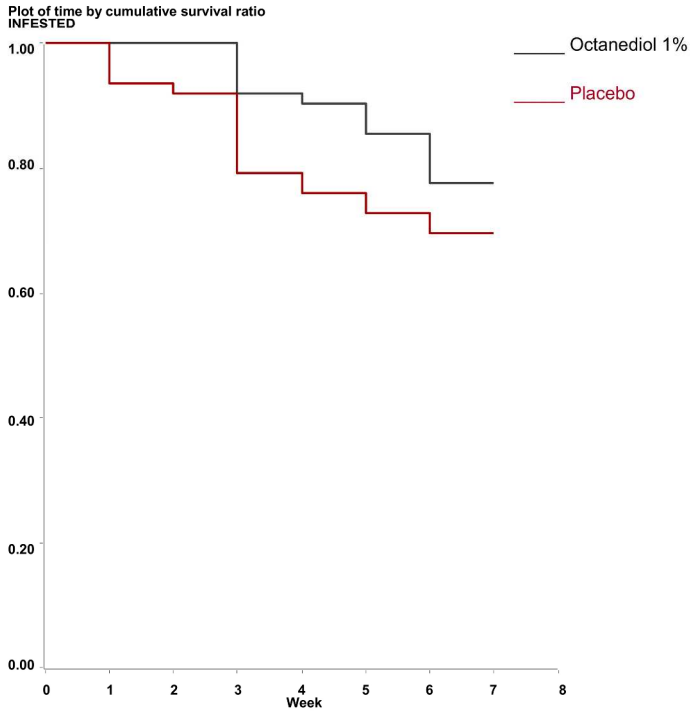
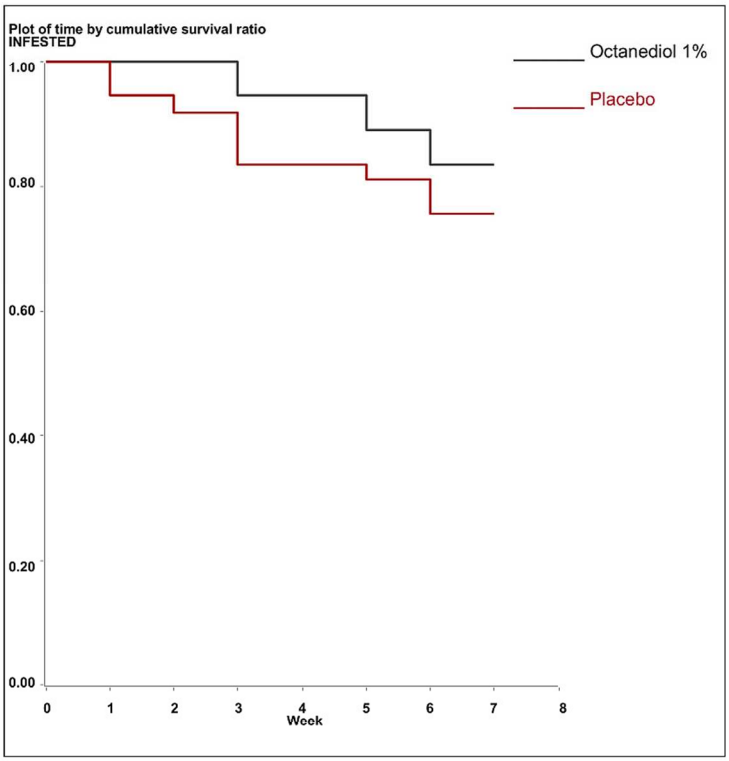
Figure 3. Kaplan-Meier plot of time to infestation Intention to treat population



Kaplan-Meier plot of time to infestation Intention to Treat population
279x361mm (300 x 300 DPI)

Figure 4. Kaplan-Meier plot of time to infestation Per-Protocol population



Kaplan-Meier plot of time to infestation Per-Protocol population
90x116mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	5, 6
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7, 8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	9, 10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10, 11
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10, 11
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	11
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10, 11
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	7, 11

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11-13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11-13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	13-14
	13b	For each group, losses and exclusions after randomisation, together with reasons	13-14
Recruitment	14a	Dates defining the periods of recruitment and follow-up	13
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	16
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	14, 17-21
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	17-21
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	17-21
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	22
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	22-24
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	22-24
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	24-25
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	Supplementary file
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	26

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.